Poster

[P25-10] P25-10: Oncologic drugs (2)

Chair: Takuya Iwamoto, Japan

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[P25-10-1] Retrospective investigation of concomitant medications as potential risk factors for sever neutropenia in cancer patients treated with carboplatin and paclitaxel combination therapy

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Background

Paclitaxel and carboplatin combination (TC) therapy is used for the treatment of various solid tumors, including lung cancer and ovarian cancer. Chemotherapy-induced severe neutropenia leads to critical issue in infection, delay of chemotherapy schedule and dose reduction. Paclitaxel is transported into hepatocytes via organic anion transporting polypeptide (OATP) 1B1 and 1B3, and is mainly inactivated by cytochrome P450 (CYP) 2C8 and 3A4. Current two case reports suggest caution for high toxicity caused by drug-drug interaction with paclitaxel and additional medications, amiodarone and clopidogrel. However, there are few reports about the effects of concomitant medications on developing severe neutropenia in patients receiving TC therapy. We performed a retrospective study to determine risk factors for neutropenia in cancer patients receiving TC therapy, furthermore conducted *in vitro* study.

Methods

A retrospective study using medical records was carried out on 174 patients treated with TC therapy in Shiga University of Medical Science Hospital since Oct. 2009 to Oct. 2015. Severity of neutropenia was determined by Common Terminology Criteria for Adverse Events ver 4.0 based on the nadir of absolute neutrophil count data between day 0 and day 21. *In vitro* study, uptake of paclitaxel by OATP1B3 was evaluated using stable-transfected human embryonic kidney 293/OATP1B3 cells. CYP2C8 activity was evaluated using recombinant CYP2C8.

Results

In 174 patients, 55 (31.6%) patients developed grade 3 or 4 neutropenia. Multivariate analysis showed that age (odds ratio [OR], 1.067 per year increase; 95% confidence interval [CI], 1.015–1.121, p = 0.010), total bilirubin value (OR, 7.854 per 1 mg/dL increase; 95% CI, 1.380–44.71, p = 0.020) and prescription of magnesium oxide (OR, 3.042 increase with prescription; 95% CI, 1.324-6.990, p = 0.009) were significantly associated with grade 3 or 4 neutropenia. In addition, all patients who prescribed candesartan cilexetil (N = 6) developed severe neutropenia. *In vitro* study, candesartan significantly inhibited OATP1B1-mediated uptake and CYP2C8-mediated metabolism of paclitaxel in candesartan concentration-dependent manner, but hardly inhibited the uptake and metabolism at clinically relevant concentrations.

Conclusions

Our study suggests that prescription of magnesium oxide and candesartan cilexetil are potential risk factor for severe neutropenia in patients receiving TC therapy.